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Drug Delivery Systems for Imaging and Therapy of Parkinson's Disease

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Abstract: *Background*: Although a variety of therapeutic approaches are available for the treatment of Parkinson's disease, challenges limit effective therapy. Among these challenges are delivery of drugs through the blood brain barier to the target brain tissue and the side effects observed during long term administration of antiparkinsonian drugs. The use of drug delivery systems such as liposomes, niosomes, micelles, nanoparticles, nanocapsules, gold nanoparticles, microspheres, microcapsules, nanobubbles, microbubbles and dendrimers is being investigated for diagnosis and therapy.

Methods: This review focuses on formulation, development and advantages of nanosized drug delivery systems which can penetrate the central nervous system for the therapy and/or diagnosis of PD, and highlights future nanotechnological approaches.

Results: It is esential to deliver a sufficient amount of either therapeutic or radiocontrast agents to the brain in order to provide the best possible efficacy or imaging without undesired degradation of the agent. Current treatments focus on motor symptoms, but these treatments generally do not deal with modifying the course of Parkinson's disease. Beyond pharmacological therapy, the identification of abnormal proteins such as α-synuclein, parkin or leucine-rich repeat serine/threonine protein kinase 2 could represent promising alternative targets for molecular imaging and therapy of Parkinson's disease.

Conclusion: Nanotechnology and nanosized drug delivery systems are being investigated intensely and could have potential effect for Parkinson's disease. The improvement of drug delivery systems could dramatically enhance the effectiveness of Parkinson's Disease therapy and reduce its side effects.

Keywords: Advantages of drug delivery systems, drug delivery systems, imaging of Parkinson's disease, liposomes, microbubbles, nanoparticles, therapy of Parkinson's disease.

INTRODUCTION

Parkinson's disease (PD), also known as idiopathic or primary parkinsonism is a progressive degenerative disorder of the central nervous system [1, 2]. Although its mechanisms and causes are not clearly defined, it is thought that the motor symptoms of PD result from the death of dopamine-generating cells in the substantia nigra, a region of the midbrain, inducing a dopamine deficiency which is the hallmark feature of this disease. PD is most commonly seen in people who are middle aged or elderly [3]. Recent findings showed that about 1 in every 200 people between 60 and 69 years of age, about 1 in every 100 people between 70 and 79 years, and about 1 in every 35 people between 80 and 89 years of age suffer from PD in the United States (US) and Western Europe [4, 5].

PD takes its name from James Parkinson, an English physician who published a description of the disease in 1817. PD is among the most common geriatric neurodegenerative disorders [6]. Environmental toxins, genetic factors, and oxidative stress may be involved in the development of PD. Pesticide exposure has been linked to a significantly increased risk of PD [7]. Mutations in the α-synuclein protein gene such as A30P and A53T can induce PD in animal models by causing intra-cellular α-synuclein aggregation and deposition to form Lewy bodies which are significant signs of PD [8]. Dopaminergic loss in the basal ganglia can be detected in animal models such as mice and flies that express these abnormal proteins [9]. Another mechanism of PD is assumed to be the formation of unstable free radicals, which are byproducts of oxidative stress contributing to nerve cell death. MTH1 suppresses cell death due to oxidative stress in PD patients [9-13].

In PD, most of the dopamine signals from the substantia nigra are lost. The nigro-striatal dopaminergic pathway travels from the substantia nigra to brain regions including the corpus striatum (caudate – putamen), globus pallidus and thalamus. It controls movement and balance, and is severely affected in PD. Dopamine is secreted from membrane storage vesicles in the presynaptic neurons and activates postsynaptic dopamine receptors to induce its physiologic effects [14]. Dopamine is directly broken down into inactive metabolites by the enzymes monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT). In most areas of the brain, including the striatum and basal ganglia, dopamine is

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inactivated by re-uptake mechanism *via* the dopamine transporter (DAT) and then enzymatic breakdown by MAO [15].

Most of the symptoms of PD are related to motor functions because dopamine is essential for transmitting electrical signals for sustaining normal physical motion [16, 17]. At early stages of PD, the most commonly seen symptoms are movement-related such as tremor, rigidity, slowness of movement, and difficulty walking. As the disease progresses, thinking and behavioral problems may arise, and dementia can occur in the advanced stages of the disease [18]. Additionally, depression can be seen as a psychiatric symptom in PD patients. The mechanism of depression in PD is not clear, however it may be due to the deficiency of multiple transmitters in mesocortical monoaminergic systems containing dopaminergic, noradrenergic and serotonergic projections [19-21]. Other PD symptoms may include sensory and emotional issues such as hallucinations and sleep disturbances. Subtle cognitive deficits, especially frontal lobe executive dysfunction, may be detected in patients with early PD through sensitive neuropsychological testing [22, 23]. Postural hypotension can also be seen, particularly in PD patients with dementia [24].

One issue in the pharmacologic treatment of neuro-degenerative diseases and brain related disorders is the difficulty for drugs to penetrate the blood brain barier (BBB) and deliver a sufficient dose to the brain target tissue without metabolization [25, 26]. This difficulty stems from the protective barriers surrounding the brain such as the BBB and the blood-cerebrospinal fluid barrier (B-CSFB) formed by tight endothelial cells junctions [17, 26-29]. Passage of substances through the BBB can be increased in several cases such as inflammation and neoplasia due to increased vascular penetration and leakage. Because a limited number of substances can penetrate the BBB freely, it is very important to develop drug delivery systems with properties that allow effective treatment [25]. Factors that limit the ability to deliver therapeutic agents to the brain tissue of PD patients also limit the ability to deliver substances that would improve imaging and diagnosis of PD.

PD Diagnosis and Imaging

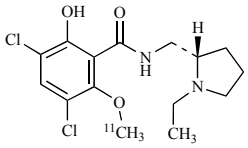
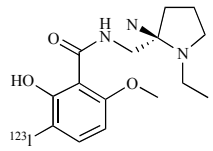
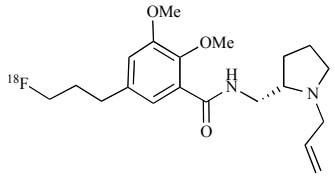
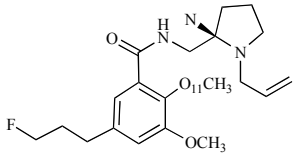
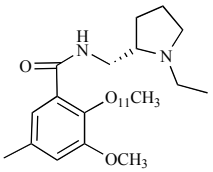
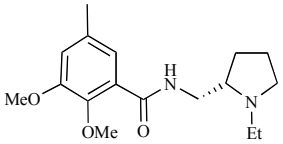
The ability to diagnose PD before the appearance of typical symptoms such as slowed movements, muscle rigidity, and deficits in posture could be an important step toward improving the quality of life for PD patients. Early diagnosis at the level of molecular alterations before the onset of symptoms can be approached by molecular imaging [31]. Molecular imaging can provide quantification of gene and protein functions, and thus provide better information about the molecular pathophysiology of a specific disease, on the protein-protein interactions and signal transduction pathways [30, 31]. Initially it is neccessary to define molecular targets, such as receptors, transporters, enzymes or abnormal proteins in order to specifically study a disease. Generally, an age-dependent decrease is observed in the density of dopamine transporters in patients suffering from PD [32, 33]. A variety of specific imaging radioligands have been developed and investigated in order to improve the early diagnosis, follow-up and treatment of PD.

The dopamine D2 and D3 receptors have been proposed as useful targets in the field of PD. ^{123}I-iodolisuride was synthesized for specific SPECT imaging of D2 receptor [34]. Other D2 receptor specific radioligands are ^{11}C-(S)-(-)-N-((1-ethyl-2-pyrrolidinyl)methyl)-5-bromo-2-hydroxy-3-methoxybenzamide) ([^{11}C]FLB) and ^{76}Br-(S)-(-)-N-((1-ethyl-2-pyrrolidinyl)methyl)-5-trimethyltin-2,3-dimethoxybenzamide ([^{76}Br]FLB) [35, 36], ^{18}F-N-methyl-benperidol ([^{18}F]FMB) [37], Epidepride, (S)-(-)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-[^{123}I]iodo-2,3-dimethoxybenzamide [38], ^{18}F-Fallypride ((N-[(1-allyl)-2-pyrrolidinyl)methyl]-5-(3-^{18}F-fluoropropyl)-2,3-dimethoxy-benzamide) (^{18}F-FP) [39], ^{18}F-Desmethoxyfallypride (^{18}F-DMFP) [40], [^{11}C]Raclopride [41], ^{123}I-Iodobenzamide ([^{123}I]IBZM) [42], [^{11}C](+)-4-Propyl-3,4,4a,5,6,10b-hexahydro-2H-naphtho[1,2-b][1,4]oxazin-9-ol ([^{11}C]-(+)-PHNO) [43]. The name, molecular structure and synthesis process of some of D2/D3 receptor radioligands under research are provided in Table **1**.

Dopamine transporter (DAT) imaging can be performed with radiolabeled cocaine derivatives such as 3 beta-(4-iodophenyl)tropan-2 beta-carboxylic acid methyl ester ([^{125}I]RTI-55) [44] and (E)-N-(3-bromoprop-2-enyl)-2β-carbomethoxy-3β-4'-tolyl-nortropane ([76Br]PE2Br) [45]. [^{125}I]RTI-55 has demonstrated a high binding affinity to striatum and DAT. It also has a high binding affinity to cerebral cortex [44]. [^{76}Br]PE2Br was obtained by electrophilic substitution with a radiochemical yield of 80%. It demonstrated a high uptake in the striatum (2.2% ID/g tissue at 15 min post-injection). A specific accumulation ratio of 6 between the striatum and cerebellum was observed for [^{76}Br]PE2Br at 1 h p.i. [45]. Some tropane analogs such as ^{18}F-fluorinated-N-3-fluoropropyl-2-β-carboxymethoxy-3-β-(4-iodophenyl)nortropane ([^{18}F]FP-CIT) and ^{99m}Tc-TRODAT-1 can also be used for DAT imaging [31]. The effectiveness of another DAT ligand, (E)-N-(3-iodoprop-2-enyl)-2β-carbomethoxy-3β-(4'-methylphenyl)nortropane (PE2I), was investigated by Guilloteau *et al*. [46]. PE2I demonstrated good affinity for the DAT (4 nM) and it is one of the most selective DAT ligands. [^{125}I]PE2I showed very intense and selective binding in the basal ganglia of postmortem human brains. It is a very efficient and specific radiotracer for DAT autoradiography studies [46]. Other DAT radioligands include ^{18}F-(E)-N-(3-iodoprop-2-enyl)-2β-carbofluoroetoxy-3β-(4-methyl-phenyl)nortropane (^{18}F-FE-PE2I) [47] and 2′-[^{18}F]Fluoroethyl (lR-2-exo-3-exe)-8-methyl-3-(4-chlorophenyl)-8-azabicyclo[3.2.1]-octane-2-carboxylate [^{18}F]-FECT [48], which are potent DAT inhibitors. The inhibitory constant (Ki) of FECT for DAT was found to be 6 nM [48]. Chalon *et al*. investigated another marker for PET imaging of striatal as well as extrastriatal dopamine transporters: (E)-N-(4-fluorobut-2-enyl)-2β-carbomethoxy-3β-(4'-tolyl)nortropane (LBT-999) [49, 50]. [^{3}H]LBT-999 bound to a single site with a Kd of 9 nM *in vitro* on rat striatal membrane and with a very high selectivity for the DAT [49]. This promising marker was radiolabeled with ^{18}F or ^{11}C for PET imaging [49, 51]. The name, molecular structure, and synthesis process of some of the DAT radioligands under investigation are provided in Table **2**.

Other novel approaches have been taken for the diagnosis of PD. For example, Au-doped TiO_2 nanotube arrays were

Table 1. Some of dopamine D2/D3 receptor radioligands under research [34-43].

Radioligand	Molecular Structure	Availability
[^{11}C]Raclopride		Radiochemical synthesis
[^{123}I]IBZM ((S)-N-[(l-ethyl-2-pyrrolidinyl)methyl]-5-iodo-2-methoxybenzamide)		Commercially available
^{18}F-Fallypride		Commercially available
^{11}C-Fallypride		Commercially available
^{11}C-FLB457		Radiochemical synthesis
[$^{123/125}$I]Epidepride		Commercially available

formulated for the purpose of producing a high sensitivity photoelectrochemical immunosensor for α-synuclein detection by An *et al*. [52]. Another tool based on nanomanipulation of a single molecule of α-synuclein was designed by Yu *et al*. for characterizing the misfolding and self-assembly of α-synuclein, which has a significant role in PD [53]. An *in vitro* quantitative assay for neurotransmitters involved in PD was performed by Baron *et al*. to investigate the plasmon absorbance and Au nanoparticles, and very promising results were obtained [54].

PD Therapy

There are currently many proposed treatment regimens for PD patients. Most of the treatments are used to reduce the signs or symptoms of PD and enhance the overall quality of life for the patient [55, 56]. Surgical approaches can also be used to stimulate deep brain tissue or transplant of fetal neurons [57]. The use of deep brain stimulation was approved by the US Food and Drug Administration for the treatment of PD, in 2002, and since then almost 80,000 procedures have been administered by physicians around the world. However, this treatment is now very rare [58]. The most common, easiest, and most practical therapeutic approach for PD is drug therapy [28]. The conventional and current treatment approaches include carbidopa/ L-DOPA, dopamine agonists, monoamine oxidase type B (MAO-B) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, amantadine and anticholinergics [59]. PD treatment with dopamine agonists like oral L-DOPA or pramipexole therapy is one of the most widely used approaches [60]. L-DOPA remains the most effective, and is considered as the gold standard for PD therapy. However, its chronic use is associated with potentially disabling motor complications and side effects.

The Use of Drug Delivery Systems for Diagnosis and Therapy of PD

It may be necessary to increase the dose of drugs administered to PD patients in order to obtain sufficient therapeutic effect in the brain. This increase in dose may

Table 2. Some of DAT receptor radioligands under research [44-51].

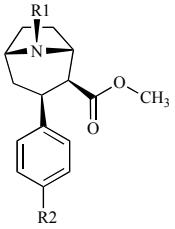
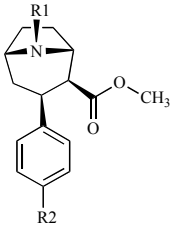
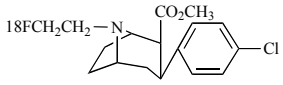
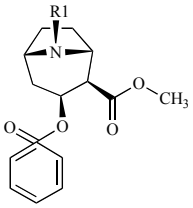
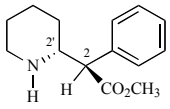
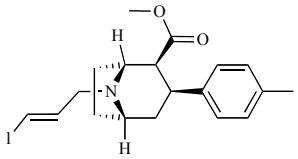
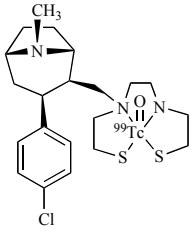
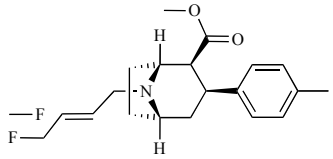
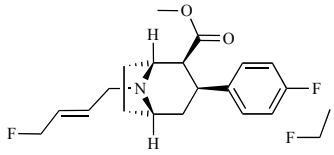
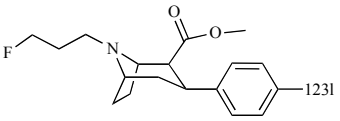
Radioligand	Molecular Structure	Availability
^{123}I-β -CIT	 [^{123}] β-CIT: R_1=CH_3, R_2=^{123}I [^{123}I] EE-CIT: R_1=$(CH_2)_2F$, R^2=^{123}I [^{123}I] EE-CIT: $R_1(CH_2)_3F$, R_2=^{123}I [^{11}C] CFT: R_1= $^{11}CH_3$, R_2= F [^{18}F] CFT: R_1= CH_3, R_2= ^{18}F	Radiochemical synthesis
^{123}I-FPCIT ((123)I-2-β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane)	 [^{123}] β-CIT: R_1=CH_3, R_2=^{123}I [^{123}I] EE-CIT: $R_1(CH_2)_2F$, R^2=^{123}I [^{123}I] EE-CIT: $R_1(CH_2)_3F$, R_2=^{123}I [^{11}c] CFT: R_1= ^{11}C H_3, R_2= F [^{18}F] CFT: R_1= CH_3, R_2= ^{18}F	Radiochemical synthesis
^{18}F-FECNT (2beta-carbomethoxy-3beta-(4-chlorophenyl)-8-(2-(18)F-fluoroethyl) nortropane)		Radiochemical synthesis
^{11}C-cocaine	 Cocaine: R_1=CH_3 [^{11}c] Cocaine R_1=$^{11}CH_3$	Radiochemical synthesis
[^{11}C]d-threo-methylphenidate	 d-threo (*2R, 2'R*)	Radiochemical synthesis
^{123}I-PE2I ((123)I-N-(3-iodoprop-2E-enyl)-2-β-carbomethoxy-3β-(4-methylphenyl) nortropane)		PE2I stannous precursor is commercially available
^{99m}Tc-TRODAT		Raw material is commercially available and radiochemical synthesis can be performed in some labs.

Table 2. contd….

Radioligand	Molecular Structure	Availability
LBT-999		Radiochemical synthesis
FBCFT (E)-fluorobutenyl substituted 4¢-halophenyl		Radiochemical synthesis
^{123}I-FP-β-CIT (DATscan®) (^{123}I-Ioflupane)		Commercially available

result in an increase in the frequency or severity of side effects. Researchers are searching for methods to increase the drug availability within the brain without increasing the drug dose. The use of nanosized drug delivery systems is a promising approach, and a number of different studies have been carried out on this issue. Advantages and disadvantages of some drug delivery systems are given in Table **3**.

The superiority of these drug delivery systems lies in their ability to improve the undesired properties of drug molecules such as bad taste and odor, low bioavailability, adverse reactions, and insufficient targeting of the desired tissue or organ [76]. The drug or molecule can be protected from undesired metabolism and enzymatic degradation [77-79]. These systems have various advantages including increases in safety, efficacy, and bioavailability, with simultaneous reductions in dose requirement, toxicity, and adverse effect. However, significant drawbacks include their expense, and the increased difficulty of their manufacture [79-81]. Drugs, molecules, or radiocontrast agents can be attached to these delivery systems and afterwards they can be actively delivered, localized, and targeted to the desired cell, tissue, or organ. Increased efficacy and safety can be achieved by controlling the release rate of the therapeutic agent, and a decreased volume of distribution can be obtained with active or passive targeted drug delivery systems by surface modification [82]. Additionally, bioavailability can be enhanced and drugs can be protected from enzymatic degradation by encapsulating in drug delivery systems [77-79].

Nanosized drug delivery systems have important advantages. The concept of nanotechnology is atributed to physicist Richard Feynman. Nanomedicine can be defined as the application of nanotechnology to health and is a relatively new field of science [83, 84]. Some examples of frequently used drug delivery systems include liposomes, niosomes, micelles, nanospheres, nanocapsules, nanoparticles, microparticles, microspheres, microbubbles, polymeric systems, dendrimers, colloidal gold, gold nanoshells, quantum dots, superparamagnetic particles, carbon nanotubes, cyclodextrins, and sphingosomes for the diagnosis and/or therapy of several diseases (Fig. **1**) [85-101].

To allow BBB penetration of these nanosized drug delivery systems, many properties can be considered including surface functionalization for targeting [102], prolonged half-life in blood circulation and avoiding RES opsonization which is called "*stealth*" effect [26]. Unlike, conventional drugs, nanosized and hydrophilic polymer coated stealth drug delivery systems tend to accumulate passively in diseased area such as sites of inflammation, infection and neoplasm [86]. Drug delivery systems can also be delivered actively with the attachment or modification of targeted ligands like mAb, antibody fragments, small peptides, vectors, or avidin-biotin complexes [79, 103].

Liposomes

Liposomes are very promising systems in both diagnostic imaging and therapy [104-106]. These systems have been popular and important in research for over 50 years after they were recognized as mimicking the behavior of natural membranes due to their phospholipid structure [107, 108]. The utilization of phosholipids is mostly due to their biocompatibility, biodegradability, non-toxicity and non-immunogenicity. These properties give liposomes tremendous value [107, 109]. Modification of the phospholipids allow liposomes to be targeted either passively by surface coating with a hydrophilic polymer and reducing particle size to nanosizes, or actively by a specific ligand conjugation [77, 96, 110-112].

For treatment of PD, a variety of liposome formulations have been prepared and evaluated. A study was performed on the use of dopamine encapsulated within liposomes containing surfactants Span 20 (S20), Span 40 (S40), Span 80 (S80), and a combination of Span 80 and Tween 80 (ST80) by Pichandy *et al*. [113]. The ST80 formulation was found to be more effective in the treatment of PD than the other formulations and a L-DOPA control solution (Syndopa), following i.p. injection in rats as determined by the reduction

Table 3. Pros and cons of some different nanosized drug delivery systems for the diagnosis or therapy of a variety of diseases [61-75].

Nanocarriers	Part.icle Size (nm)	Advantages	Disadvantages	Refs.
Liposomes, Niosomes, Sphingosomes	20-3500	May be labeled with various radionuclides. Contrast enhancement for imaging in the target and therapy enhancement.	The necessity of long time consuming radiolabeling process and carefull controllability for reproducible efficiency.	[63, 64]
Micelles	20-150 (very small)	Easily prepared and radiolabeled and removal by RES decreases depending on hydrophilic polymer shells.	The design of amphiphilic chelator should need attention.	[65]
Nanoparticles, Solid lipid nanoparticles	10-1000	These systems can be actively or passively targeted to the desired cell or tissue. They can escape from RES uptake. May be labeled with a variety of radionuclides.	Limited control of the size distribution and polydispersity.	[66]
Dendrimers	~10 (very small)	Multivalent conjugation of radionuclides, biodistribution is enhanced depending on low polydispersity and spherical shape.	Toxicity may be formed depending on positive charge of dendrimers.	[67]
Gold Nanoparticles	1-100	They have unique optical properties which is affected from shape and size. They can be used for cancer diagnosis and photothermal therapy.	It is important to discern the toxicity of the nanoparticle core and that of its capping ligands.	[68, 69]
Microbubbles	≤10000	Acts like red blood cells within the capillaries. Safer than molecular imaging modalities such as radionuclide imaging.	Have low circulation time due to rapid RES uptake. Heat increase can be formed due to increase in frequency which should be carefully monitored.	[70, 71]
Magnetic Nanoparticles	10-50	They can be functionalized and manipulated with a selective molecule and magnetic properties can be controlled with a magnetic field produced by an electromagnet or permanent magnet.	Metallic magnetic materials such as iron, cobalt and nickel are toxic and generally susceptible to oxidation. Uncoated magnetic nanoparticles should be chemically stabilized against degradation.	[72, 73]
Quantum dots	(typically <10)	Possesses long-term, multiplexed, and quantitative imaging and detection. They can be used as ultrasensitive and multicolor imaging of molecular targets.	Their delivery process across cells may be dangerous for the cell and may destroy it. In other cases a QD may be toxic for cells.	[74, 75]

of Parkinsonism's extrapyramidal side effects using an actophotometer and a rotarod. The encapsulation of L-DOPA derivatives in liposome formulation as potential prodrugs was performed by Di Stefano *et al*. for PD treatment in an attempt to decrease side effects [114]. Striatal levels of L-DOPA and dopamine demonstrated a 2.5-fold increase after i.p. administration of the liposomal formulation of the prodrug when compared with L-DOPA itself or free prodrug. In another study performed by Yurasov *et al*., a 10 fold smaller dose of L-DOPA provided effective treatment after the L-DOPA was encapsulated in nanosized, unilamellar liposomes when compared with free L-DOPA [115]. A significant decrease in the occurence of side effects was also observed with these liposomal formulations. In a rat model of PD, liposomes containing dopamine were formulated and stereotactically implanted into the corpus striatum. These liposomes resulted in a sustained release of dopamine for 40 days. Higher extracellular dopamine levels and partial behavioral recovery were achieved with dopamine liposomes when compared with control liposomes [116]. Another direct brain administration was performed by Alemdar *et al*. by formulating liposomes of immunosuppressive drugs tacrolimus and rapamycin [117]. Higher neuroprotective effect on dopaminergic neurons was obtained with liposomes when compared with the control group. It was reported that the combination of both liposomal formulations produced a synergistic effect [117].

Jain *et al*. developed charged liposomes containing dopamine HCl for the therapy of PD [118]. It was observed that dopamine was effectively delivered to the brain by passive targeting and was protected from degradation by incorporation into liposomes when compared with plain dopamine HCl, L-DOPA preparations and marketed formulation of L-DOPA containing carbidopa (Syndopa®) [118]. Other studies have found that cationic liposomes can easily cross the BBB by the mechanism of absorption mediated transcytosis [119]. Another study was performed by Amicarelli *et al*. in 1999 focussed on stereotaxic injection

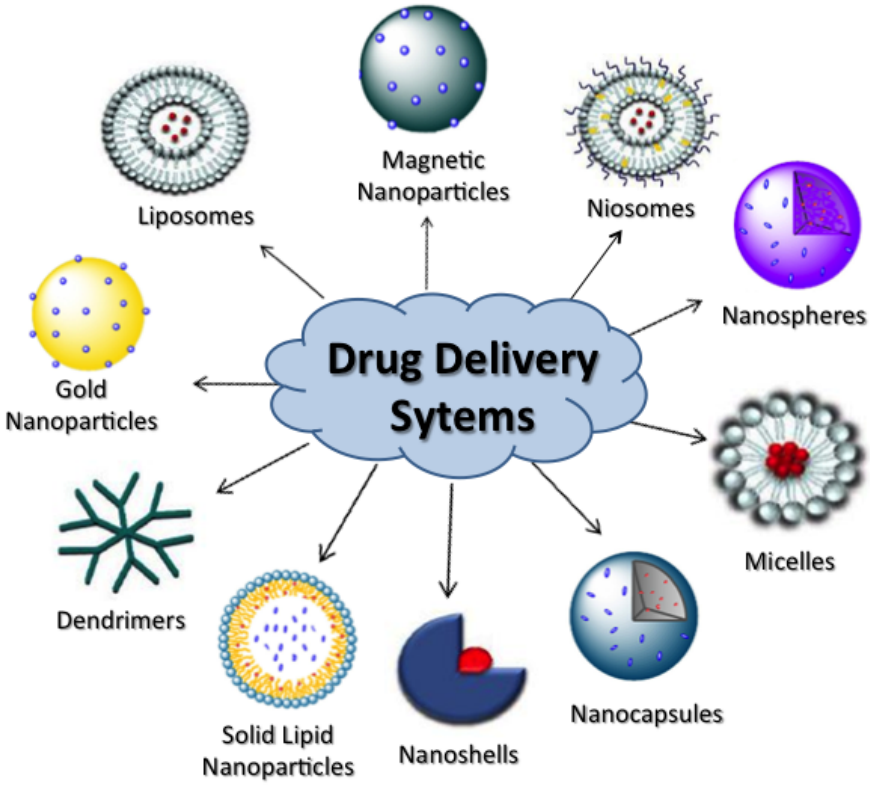


Fig. (1). Drug delivery systems for the diagnosis and/or therapy of various diseases [100, 101].

of tyrosinase encapsulated within liposomes [120]. A significant increase in dopamine level was observed in rat brain by providing L-tyrosine after correcting of the lack of tyrosine hydroxylase (TH) with the tyrosinase [120].

Liposomes containing glutathione were prepared for PD treatment and found to be effective in maintenance of intracellular glutathione and neuroprotection in mesencephalic neuronal cells. It was observed that glutathione encapsulated within liposomes could be a promising alternative when compared with non-encapsulated glutathione [121]. In a novel approach, L-DOPA was encapsulated in a stealth liposome modified with chlorotoxin, a 36-amino acid peptide. These liposomes were intented to bind specifically to gliomas, and proliferating vascular endothelial cells for PD treatment. This targeted delivery system produced successful results both *in vitro* and *in vivo*. These liposomes diminished serious behavioral disorders and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced loss of TH-positive dopaminergic neurons [122]. To overcome the oxidative stress that plays a significant role in PD, resveratrol derived from Polygonum cuspidatum was encapsulated in liposomes. When compared with resveratrol, liposome-encapsulated resveratrol produced a remarkable increase in the antioxidant capacity of nigral tissues and a remarkable decrease in the loss of nigral cells, abnormal rotational behavior and the level of total reactive oxygen species after two weeks of oral treatment [123].

Glial cell line-derived neurotrophic factor (GDNF) encapsulated liposomes for intranasal administration were found to produce neurotrophic effects in the intact substantia nigra and neuroprotective effects in the unilateral 6-hydroxydopamine (6-OHDA) model of PD [124]. Kizelsztein *et al*. prepared nanosized, PEGylated, tempamine, which is a reactive oxygen species, encapsulated liposomes for the therapy of neurodegenerative diseases including PD and MS. These liposomal systems demonstrated higher brain accumulation when compared with free tempamine and inhibited experimental autoimmune encephalomyelitis (EAE) in mice [125].

A patent was granted in 2002 for a liposome formulation which was actively targeted to a BBB receptor by a modified antibody. It was observed that this antibody fragment allowed attachment of the liposome to the wall of the endothelial cells of the BBB and release of the drug just in proximity to the receptors to provide brain penetration. Transferrin receptor, insulin receptor, insulin-like growth factor (IGF)-I receptor, IGF-II receptor [27, 126] or glucose transport receptor [127] were used for the formulation of these liposomes.

Gene therapy with chromosomal-derived forms of genes with Trojan horse liposomes was performed by Xia *et al*. [128]. It was observed that sustained replacement of striatal TH enzyme activity was produced by combination gene therapy with both cDNA and genomic forms of the TH gene administered simultaneously in experimental PD. Therapeutic genes can be successfully incorporated in Trojan horse liposomes and delivered to the brain after i.v. administration [128]. Another non-viral gene therapy study was performed by the same group related to the formulation of active targeting of rat transferrin receptor specific mAb conjugated, pTHpro-GDNF plasmid DNA encapsulated Trojan horse liposomes for PD treatment [129]. Effective and sustained therapeutic effect was achieved in 6-OHDA

lesioned rats [129]. Similarly, DNA encapsulated, nanosized, PEGylated immunoliposomes were formulated for transvascular gene therapy of PD. These liposomes can be actively targeted to the brain with the attachment of mAb specific to BBB receptors, such as the insulin receptor or transferrin receptor. It was observed that striatal TH activity was completely normalized after i.v. administration of actively targeted DNA encapsulated liposomes in 6-OHDA lesioned rats [130].

Nanoparticles

Nanoparticles are solid colloidal drug delivery systems with a particle size of 1-100 nm. They are composed of natural and synthetic polymers and ceramic or inorganic elements. Drugs can be dissolved in the composition of the nanoparticle or attached, or adsorbed, or linked on the surface of the nanoparticle [131]. Nanoparticles are one of the most commonly researched drug delivery systems for many diseases including neurodegenerative diseases. Polymeric nanoparticles can be used for BBB penetration either passively or by actively targeting molecule in the desired brain site and delivering sufficient amounts of drug [17, 132, 133]. Receptor-mediated nanoparticle delivery to the brain needs chimeric peptide technology. Generally, a BBB impermeable drug can be combined with a BBB transport vector [134, 135].

Novel α-synuclein specific mAb modified polybutyl-cyanoacrylate nanoparticles were prepared by Hasadsri *et al*. [136]. The particles were found to be very effective in treating neuronal disorders *in vitro* in cultured neurons and neuronal cell lines with an endocytosis uptake mechanism for proteins [136]. Chitosan nanoparticles with dopamine modification onto the external surface were prepared by Trapani *et al*. [137]. It was observed that dopamine loaded nanoparticles were less cytotoxic, and produced more brain accumulation and increased uptake in the striatum than DA alone after i.p. administration. Nanoparticles were also studied for their gene therapy efficacy as transfection vehicles for PD treatment. This was found to be significant for limiting the risk of excessive immune response and mutagenesis. Huang *et al*. formulated human neurotrophic factor gene encapsulated, lactoferrin-modified nanoparticles [138]. Significant improvement was observed in locomotor activity and dopaminergic neuronal decline. Lactoferrin conjugated polyethylene glycolpolylactide-polyglycolide (PEG-PLGA) nanoparticles were formulated by Hu *et al*. [139]. These brain-targeted nanoparticles were found to be more effective when compared with non-conjugated particles after i.v. administration, with almost 3 times higher accumulation observed by a fluorescent probe coumarin-6 in the striatum of 6-OHDA administered rats [139]. Another study related to lactoferrin modified nanoparticles was performed by the same group in which these liposomes were loaded with human glial cell line-derived neurotrophic factor gene (hGDNF) [140]. The lactoferrin modified nanoparticles may have potential as a nonviral gene therapy of chronic brain disorders in unilateral 6-OHDA lesioned PD model [140]. Afterwards same group developed a novel non-viral gene vector: brain targeted, lactoferrin modified hGDNF encapsulated nanoparticles for PD therapy. It was observed that multiple i.v. administration demonstrated potential results for neuroprotective effects in a rotenone-induced chronic rat model of PD [138]. The same group developed a gene delivery system comprising an angiopep, which is a specific ligand having an affinity to the low density lipoprotein receptor, conjugated to dendrigraft poly-L-lysine. Neuroprotective effects as evidenced by improved locomotor activity and apparent recovery of dopaminergic neurons in rats was achieved in rotenone-induced chronic model of PD [141].

Bromocriptine encapsulated solid lipid nanoparticles were formulated and evaluated for their antiparkinsonian effect. When compared with free bromocriptine, bromocriptine encapsulated solid lipid nanoparticles showed a prolonged release for 48 h and were found to be very effective in 6-OHDA lesioned hemiparkinsonian rats [142]. Other bromocriptine encapsulated chitosan nanoparticles were formulated by Md *et al*. by ionic gelation method for intranasal application [143]. It was observed that selective degeneration of the dopaminergic neurons in haloperidol-treated mice was reverted by bromocriptine loaded chitosan nanoparticles and it was found effective in PD therapy [143]. Odorranalectin conjugated poly(ethylene glycol)–poly(lactic-co-glycolic acid) (PEG–PLGA) nanoparticles were developed to reduce the immunogenicity of lectine and to improve the nose to brain ratio of drug delivery. It was observed that the brain delivery of these nanoparticles was enhanced after nanoparticle conjugation. The therapeutic effect of nasal delivery of urocortin peptide conjugated nanoparticles was demonstrated by increased brain delivery in hemiparkinsonian rats [144].

Tsai *et al*. developed solid lipid nanoparticles emulsified with glyceryl monostearate or polyethylene glycol monostearate which encapsulated apomorphine for oral administration to increase its oral bioavailability [145]. It was observed that the number of rotations increased significantly and the bioavailibity of apomorphine was increased 12-13 times higher with the use of these solid lipid nanoparticles in 6-OHDA lesioned PD rats [145].

BBB delivery of nanoparticles can also be investigated by intranasal administration. Ropinirole hydrochloride loaded chitosan mucoadhesive nanoparticles were formulated for intranasal drug delivery for PD therapy. After intranasal administration of ropinirole hydrochloride loaded chitosan nanoparticles, a sustained release profile was achieved after about 18 h and enhanced brain accumulation was observed compared to that seen with ropinirole hydrochloride solution by gamma scintigraphy after ^{99m}Tc radiolabeling [146]. L-DOPA encapsulated nanoparticles were formulated for intranasal administration and their effectiveness was compared with the standard form for PD treatment. L-DOPA encapsulated nanoparticles demonstrated higher effective half-life, bioavailability, brain delivery, and efficacy according to motor movements and behavior [147].

VP025 (Vasogen Inc.) was prepared as a novel phospholipid nanoparticle incorporating phosphatidylglycerol in order to obtain neuroprotective effect. Fitzgerald *et al*. showed that VP025 has a potential therapeutic effect on the impairment of dopaminergic motor activity and dopamine deficit induced by proteasome inhibition in rat model of PD [131, 148]. The effect of VP025 was also evaluted in 6-OHDA administered

PD rats by Crotty *et al*. [149]. It was observed that VP025 inhibited dopaminergic neuron loss in 6-OHDA administered rats and it has a potential neuroprotective effect [149].

Nicotine encapsulated poly(lactic-co-glycolic)acid (PLGA) nanoparticles were prepared by Tiwari *et al*. [150]. It was reported that the neuroprotective effect of nicotine was enhanced by preparation of its nanoparticles depending on the results of oxidative stress and apoptosis in MPTP-treated mice.

Another study was performed by Liu *et al*. with the formulation of a brain targeted gene delivery system based on a non-viral gene vector: a rabies virus glycoprotein peptide with 29 amino-acid linked to dendrigraft poly-L-lysines which can pass the BBB by specific receptor mediated transcytosis [151]. The effect of silencing caspase-3 genes by RNA interference in inhibiting the activation of caspase-3, which has a significant role in PD treatment was investigated. This nanoparticle was found to be promising when applied i.v. in a multiple dose regimen because it reduced the activated caspase-3 levels, causing a significant improvement in locomotor activity and rescue of dopaminergic neuronal loss in PD treatment of rats [151].

Dopamine-loaded chitosan nanoparticles were formulated for the therapy of PD [152]. Brain delivery of dopamine in different concentrations after i.p. administration was accomplished by formulating chitosan nanoparticles with varying concentrations of dopamine. It was found that chitosan nanoparticles with dopamine at a concentration of 6-12 $mg.kg^{-1}$ produced a dose dependent increase in dopamine in the tissue [137].

Rhodamine-B conjugated multimodal iron oxide nanoparticles were formulated by Sibov *et al*. to label mesenchymal stem cells [153]. It was observed that about 5×10^5 labeled cells were efficiently imaged with MRI shortly after infusion in the brain striatum of a rat model of PD [153]. A fluorescent nanoparticle with multiple functionalization of highly fluorescent core/shell CdSe/CdS quantum rods for specific targeting and controlled release of attached dopamine was prepared for both diagnosis and therapy. It was reported that PEGylation provided biocompatibility, a carbohydrate shell covering, and specific GLUT-1 recognition which is essential for both diagnosis and therapy of neurodegenerative diseases such as PD [154].

Gold Nanoparticles

Gold nanoparticles (Au nanoparticles) are used less frequently than other drug delivery systems. However, a significant amount of research has been performed on these systems. Gold nanoparticles (colloidal gold) have applications both in biology (*e.g*. bio-imaging) and technology (eg. Photonics) due their unique optical properties arising after the interaction of light with electrons on the nanoparticle surface [155]. These systems were investigated as drug carriers, photothermal agents, contrast agents and radiosensitisers for both diagnosis and therapy of diseases. Their use in a variety of diseases, including cancer, has been investigated [156-158].

The use of gold nanoparticles was investigated for the diagnosis of PD. As described previously, the aggregation of α-synuclein is a potential cause of PD. The use of gold nanoparticles provides quantitative colorimetric detection of neurotransmitters such as dopamine, L-DOPA, epinephrine, and norepinephrine by plasmon absorbance. Tyrosinase oxidizes tyrosine to L-DOPA and its activity can be probed by neurotransmitter-mediated growth of gold nanoparticles. The activity of tyrosinase is crucial for PD detection [54]. A study was performed by Yang *et al*. to investigate the ability to adsorb α-synuclein onto positively charged poly(allylamine hydrochloride) coated gold nanoparticles [159]. It was observed that the access of α-synuclein to enzymatic attack was altered and the conformation was changed after adsorbed onto gold nanoparticles [159].

Gold-doped TiO_2 nanotube arrays were prepared by An *et al*. to design a photoelectrochemical immunosensor for the detection of α-synuclein which is important in PD diagnosis [160]. They produced highly ordered TiO_2 nanotubes by using an electrochemical anodization technique on pure Ti foil [160].

Microspheres, Microbubbles and Nanobubbles

Microspheres can be defined as small spherical particles with a diameter ranging from 1 μm to 1000 μm. Sometimes microspheres are called microparticles [161]. The neuroprotective effect of lipid-coated glial cell derived neurotrophic factor (GDNF) microspheres was investigated in a 6-OHDA injected rat model of PD [145]. It was observed that after intrastriatal administration of lipid coated GDNF microspheres and a low frequency ultrasound stimulation, GDNF levels were increased. A neuroprotective effect was obtained with striatal administration of lipid coated GDNF microspheres as evidenced by a reduction in apomorphine induced rotations and an increase in striatal dopamine and nigral TH levels in PD rats [162]. Another similar study was performed by Garbayo *et al*. related to the formulation of N-glycosylated recombinant GDNF encapsulated microspheres for PD treatment [163]. This formulation was found to have suitable release kinetics over up to 5 weeks *in vivo* and a neurorestorative effect in the rotational behaviour test and increased TH+ fiber density at the striatal level [163]. Another study was performed by Herran *et al*. evaluating the neuroregenerative effect of vascular endothelial growth factor (VEGF), GDNF encapsulated polymeric microspheres, and their combination in rats representing a severe stage of PD [164]. Higher levels of neuroregeneration/neuroreparation in the substantia nigra were obtained with the treatment of GDNF microspheres and with both VEGF and GDNF microspheres when compared with control group, evidenced by the rotation behavior test and surviving TH+ cells [164]. The effect of intrastriatal administration of GDNF encapsulated microspheres was also evaluated by Gouhier *et al*. by using rotameter, TH immunohistochemistry, and PE2I-labeled DAT density [165]. GDNF encapsulated microspheres were found to be neuroprotective, and PE2I was also found to be an effective SPECT and PET imaging radiotracer for both the diagnosis and follow up of PD [165].

Rotigotine is a non-ergoline D3/D2/D1 dopamine agonist. Rotigotine loaded poly(lactide-co-glycolide) containing micro-spheres were prepared and their subchronic toxicity was

studied by Ye *et al*. using a consecutive weekly dosing schedule for 3 months followed by a 1-month recovery period [166]. It was reported that rotigotine microspheres demonstrated a high level of safety in Sprague Dawley rats [166]. Rotenone microspheres were successfully encapsulated and characterized by Huang *et al*. for a different purpose [167]. Typical PD symptoms were observed with the use of these systems in rats as demonstrated by cataleptic behavior and TH immunohistochemistry tests. Rotenone encapsulated microspheres induced degeneration of dopamines in the striatum and substantia nigra in rats [167].

Polybutylene succinate microspheres were formulated by double emulsion solvent evaporation technique (W/O/W) for the therapy of PD. Potential results were obtained with an encapsulation efficiency of 53.93% and 62.28% for porous and smooth microspheres, respectively. A sustained release was achieved after a burst effect with the use of Poly(butylene succinate) microspheres [168]. Rasagiline mesylate encapsulated microspheres were prepared according to the O/W emulsion and W/O/W double emulsion method by Fernandez *et al*. to obtain sustained release in PD treatment [169]. The microsphere prepared by the O/W emulsion technique appear to provide superior results. Although rasagiline mesylate demonstrated a robust effect for both formulations after 45 days, rasagiline mesylate encapsulated microspheres showed controlled release following administration every 2 weeks when compared with its administration in solution [169]. L-DOPA prodrug L-dopa-α-lipoic acid (LD-LA) was encapsulated into biodegradable polymeric microspheres for the purpose of overcoming fluctuations in the concentration of the drug in plasma. The encapsulated drug was theorized to have the advantages of a longer plasma half-life than that of L-DOPA, lower susceptibility toward enzymatic conversion by L-DOPA degrading enzymes such as catechol-O-methyltransferase and monoamine oxidase, and higher lipophilicity than L-DOPA which would facilitate BBB penetration. It was observed that sustained release of LD-LA encapsulated polymeric microspheres induced continuous dopaminergic stimulation for up to 4 days after a single administration for PD treatment [170].

Colloidal bubbles are emerging as important contrast agents for imaging and carriers for targeted drug delivery [171-173]. Microbubbles are bubbles with a diameter ranging between 1 μm and 1000 μm [174]. They can be used in medical diagnostics as a contrast agent for ultrasound imaging [175]. The gas (air or perfluorocarbon) filled microbubbles oscillate and vibrate when a sonic energy field is applied and they may reflect ultrasound waves. In this way microbubbles or nanobubbles can be distunguished from other surrounding tissues. Microbubbles and nanobubbles may be used as drug delivery systems [176]. To exist in the aqueous media and stay stable, microbubbles and nanobubbles need to be stabilized against surface tension with a stabilizing shell [176, 177]. Nanobubbles are very similar to microbubbles: the only difference is their smaller particle size. This smaller particle size gives nanobubbles some advantages such as high surface area and high stability in the liquid phase [178]. Both apomorphine HCl and base encapsulated, acoustically active perfluorocarbon nanobubbles were formulated for the therapy of PD. Both apomorphine HCl and base encapsulated perfluorocarbon nanobubbles demonstrated delayed and sustained release profiles. While a 2-4 fold enhancement was observed in apomorphine HCl release, a decrease was observed in apomorphine base release with ultrasound application when compared with the non-ultrasound group [179].

Dendrimers

Dendrimers are repetitively branched molecules [180, 181]. Dendrimers are composed of compounds having unique properties: they are typically monodisperse and symmetric around the core, and generally have a three dimenional structure. Their size ranges from 1 -100 nm. Dendron is the small single structure of a dendrimer, comprising only a single, chemically addressable group called a focal point. Dendrimers are simply composed of the addition of layers of branching groups in which each new layer is defined as the generation [182]. Due to the unique characteristics, dendrimers can act as a particulate system while retaining its polymeric properties [183]. Bioactive agents such as antiparkinson agents, psychotics, analgesics, opioids, neurotoxins, hypnotics, tranquilizers, and anti-convulsants can be loaded for brain penetration [184].

Dendrimers have a variety of applications in drug delivery and imaging. A study was performed by Kecskes *et al*. related to the formulation of G protein coupled receptor ligand-dendrimer (GLiDe) conjugates from an adenosine receptor antagonist for the diagnosis or therapy of PD and some other diseases [185]. It was reported that effective multivalent dendrimeric derivatives of adenosine receptor antagonists were synthetized and very promising results were obtained [185].

Some disorders are believed to be related to fibrillar aggregation of proteins. These proteins are Aβ peptide in Alzheimer's Disease, α-synuclein in PD, amylin in type II diabetes, β2-microglobulin in dialysis-related amyloidosis, and prion proteins in Creutzfeldt-Jakob disease (CJD). A study was performed by Rekas *et al*. to determine the effect of polyamidoamine (PAMAM) dendrimers (generations G3, G4 and G5) on the fibrillation of α-synuclein, which is related with neurological disease formation [186]. It was observed that PAMAM significantly induced the breakdown of pre-existing α-synuclein fibrils and inhibits formation of β-sheets [186]. Another study related to the evaluation of the effect of viologen-phosphorus dendrimers in the fibrillation process of α-synuclein was performed by Milowska *et al*. [187]. Vpd-1 dendrimer comprising phoshonate groups on the surface were found very effective. It was observed that viologen-phosphorus dendrimers can inhibit α-synuclein formation and this may be potentially used as regulating agent in neurodegenerative diseases such as PD [187].

CONCLUSION

The use of drug delivery systems such as liposomes, niosomes, nanoparticles, microspheres, microbubbles, nanobubbles and dendrimers has the potential to have significant effects for drug delivery in PD. A large number of papers have highlighted the potential importance and

effectiveness of colloidal drug delivery systems in both imaging and therapy of PD. Active targeting by ligand modification, enhanced BBB penetration, increased accumulation by passive targeting, controlled delivery, and sustained release can be achieved with the use of these drug delivery systems in PD therapy or diagnosis. A significant decrease in the frequency of side effects was also observed with the use of these drug delivery systems, such as parkinsonism's extrapyramidal side effects. Nanotechnology and nanosized drug delivery systems are being investigated intensely and could have potential effect in the field of neuroprotection [188]. With improvements in molecular imaging, very early diagnosis can be achieved before the initiation of motor symptoms with the help of special ligands sepecific to molecular targets such as receptors and transporters. The progress in medicine, pharmacy, biology, and chemistry illustrates the direction of the future development of a variety of drug delivery systems in BBB penetration in brain delivery for either imaging or the therapy of various central nervous system disorders, including PD [59, 189].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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